Gamma-irradiators, X-irradiators, and Radiobiology

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The University of California owns 47 Cesium or Cobalt irradiators

10 campuses and 5 medical centers

Cesium 137

- Research irradiators – 36
- Medical- blood irradiators- 6

Cobalt 60

- Research – 2
- Medical-gamma knives – 3

223,000 staff and faculty

~ 273,000 students

Slide courtesy of Carolyn Mac Kenzie
University of California, Berkeley

UC Source Replacement Faculty Working Group (WG)

Recommendations:

- **X-ray irradiators can replace cesium irradiators in many applications**. There are likely some exceptions though, such as the need for very high radiation doses or radiation exposures over a period of days, and research specifically requiring high energy gamma radiation.
- **Every established laboratory/investigator needs to empirically assess the effects to their studies** of converting from cesium to x-rays specific with their **own comparison studies.**

Slide courtesy of Carolyn Mac Kenzie
University of California, Berkeley


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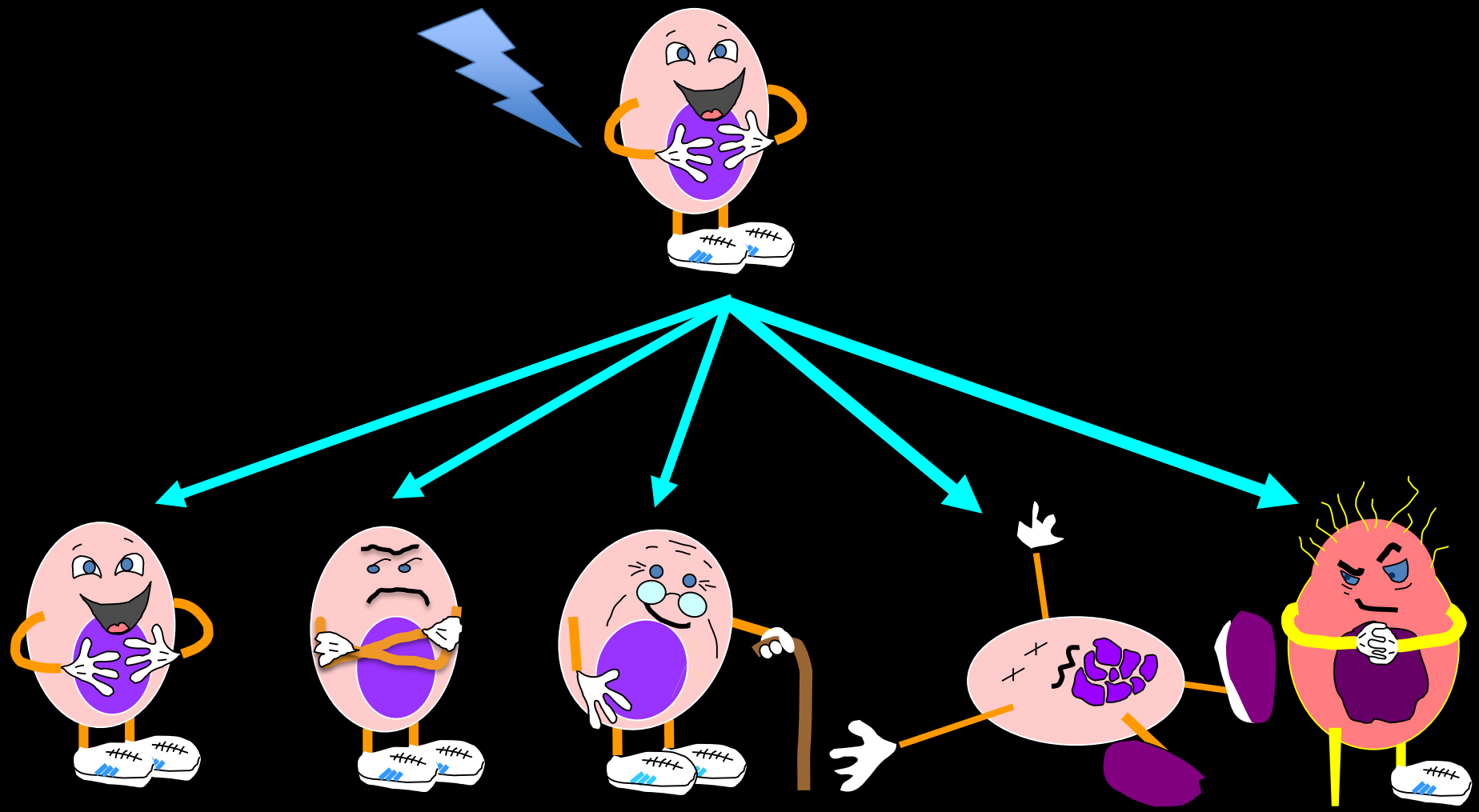
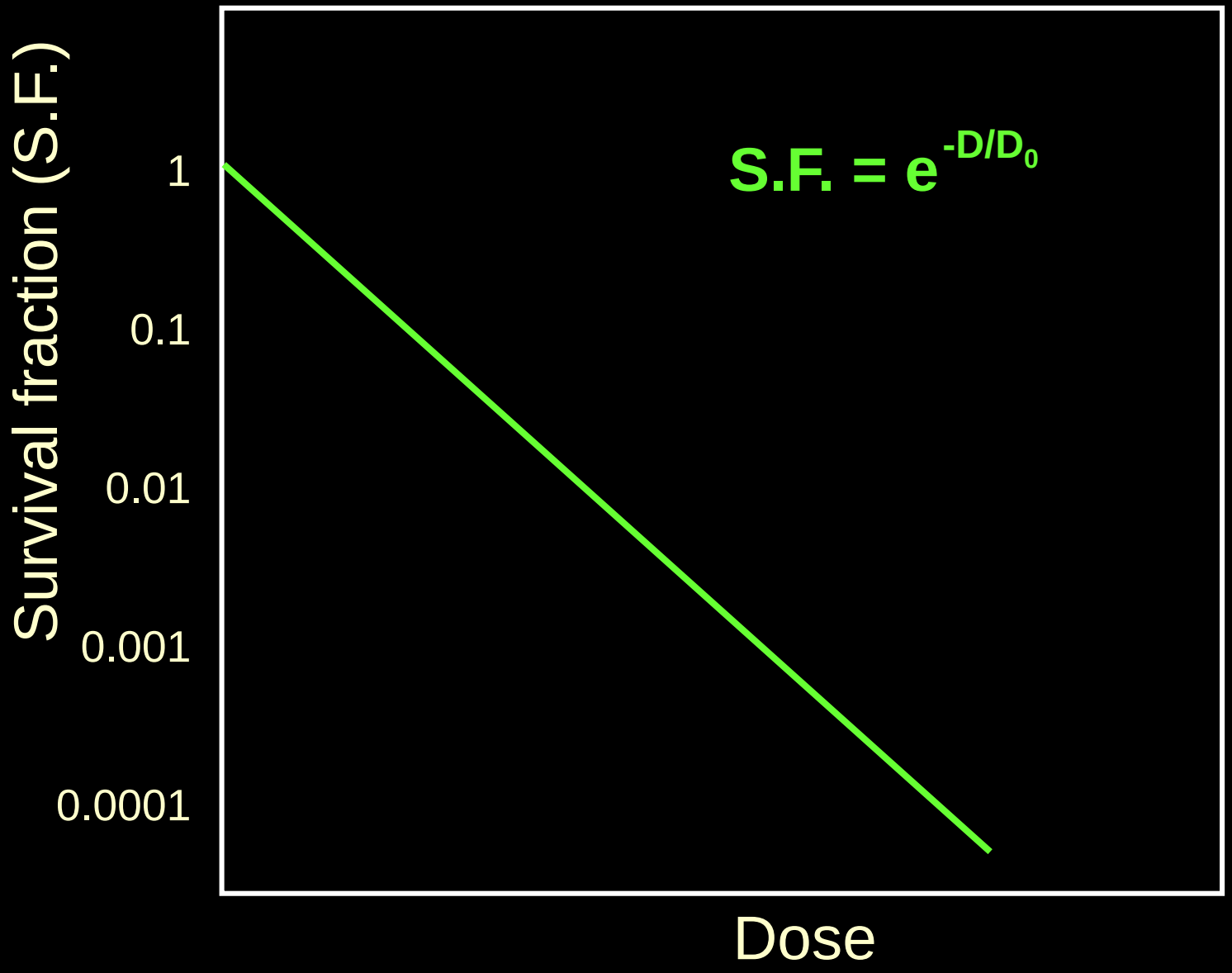
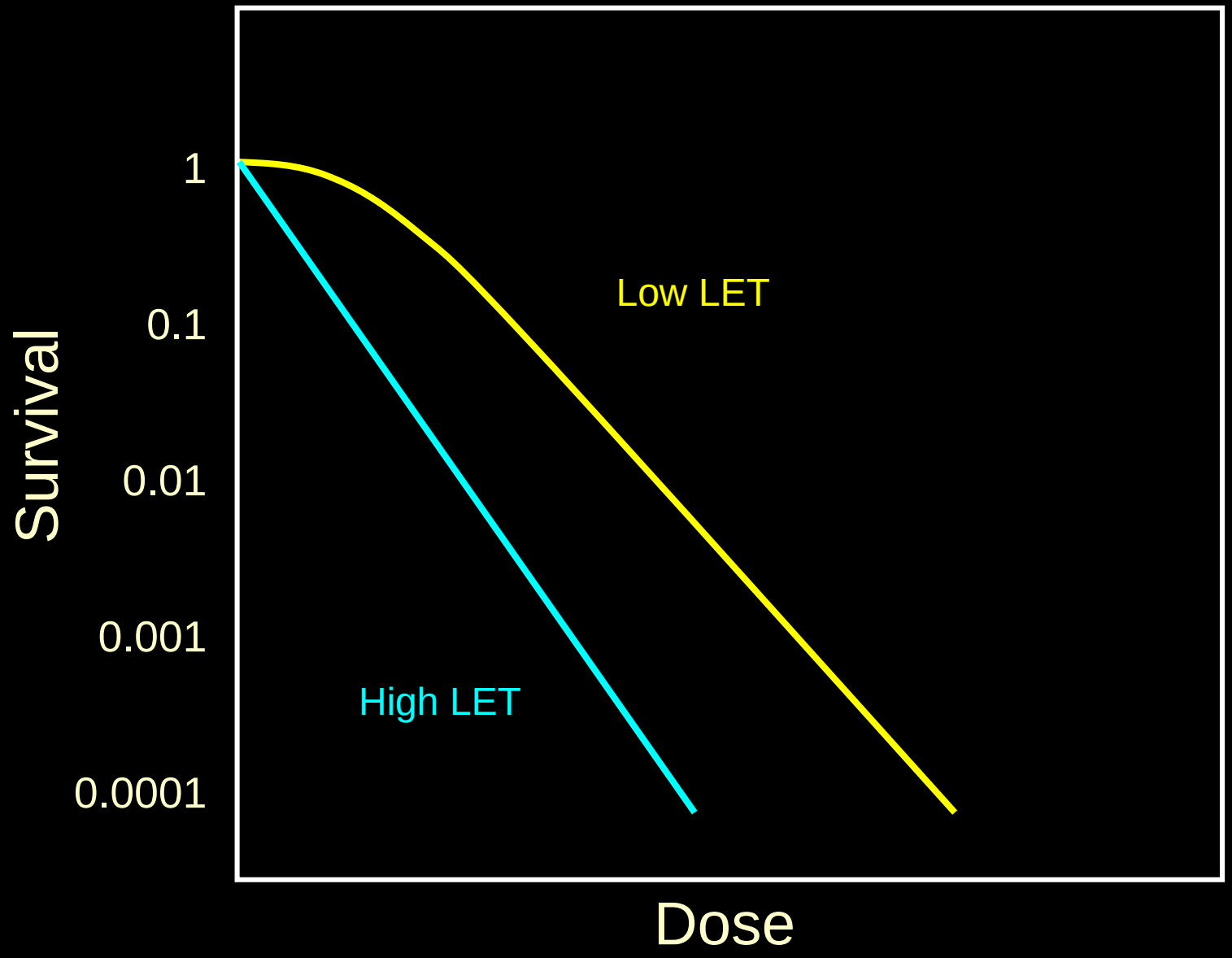
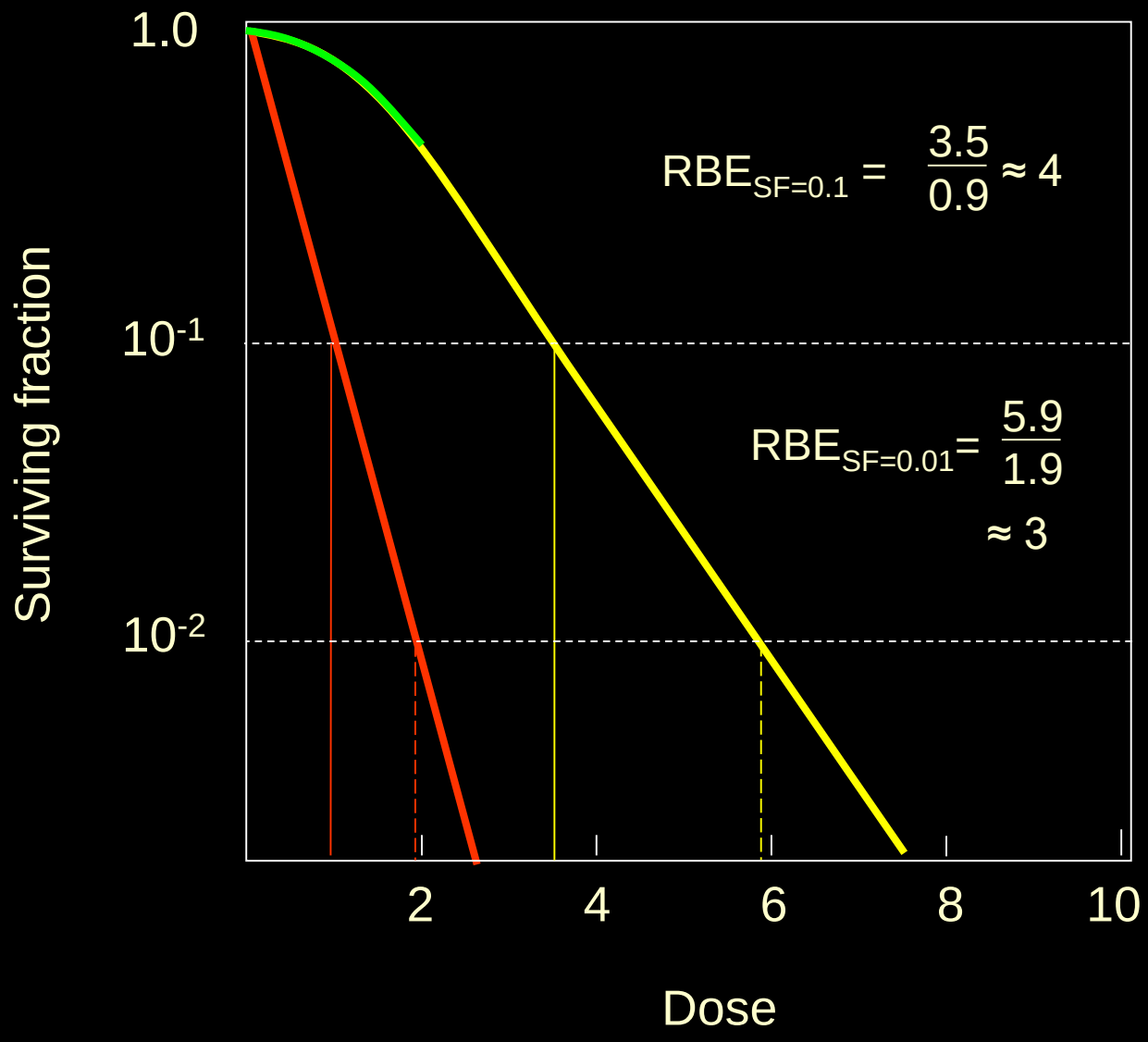
Effects of ionizing radiation on cells

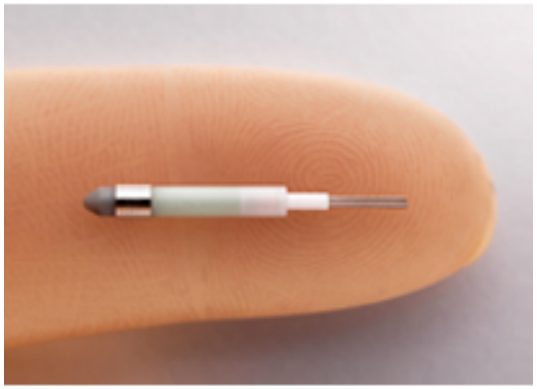


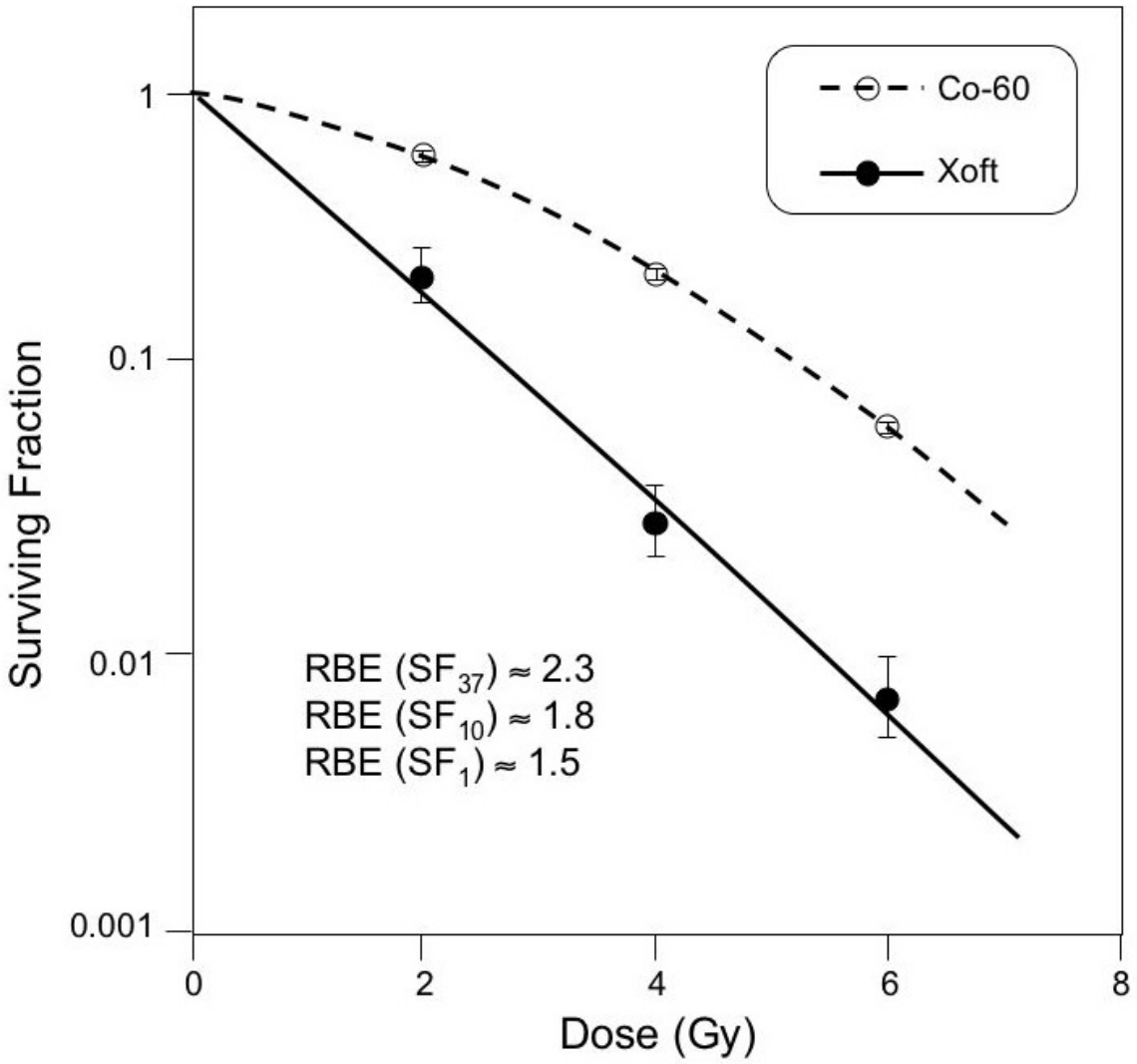

Survival fraction (S.F.)
1
0.1
0.01
0.001
0.0001
S.F. = e-D/D0
Dose

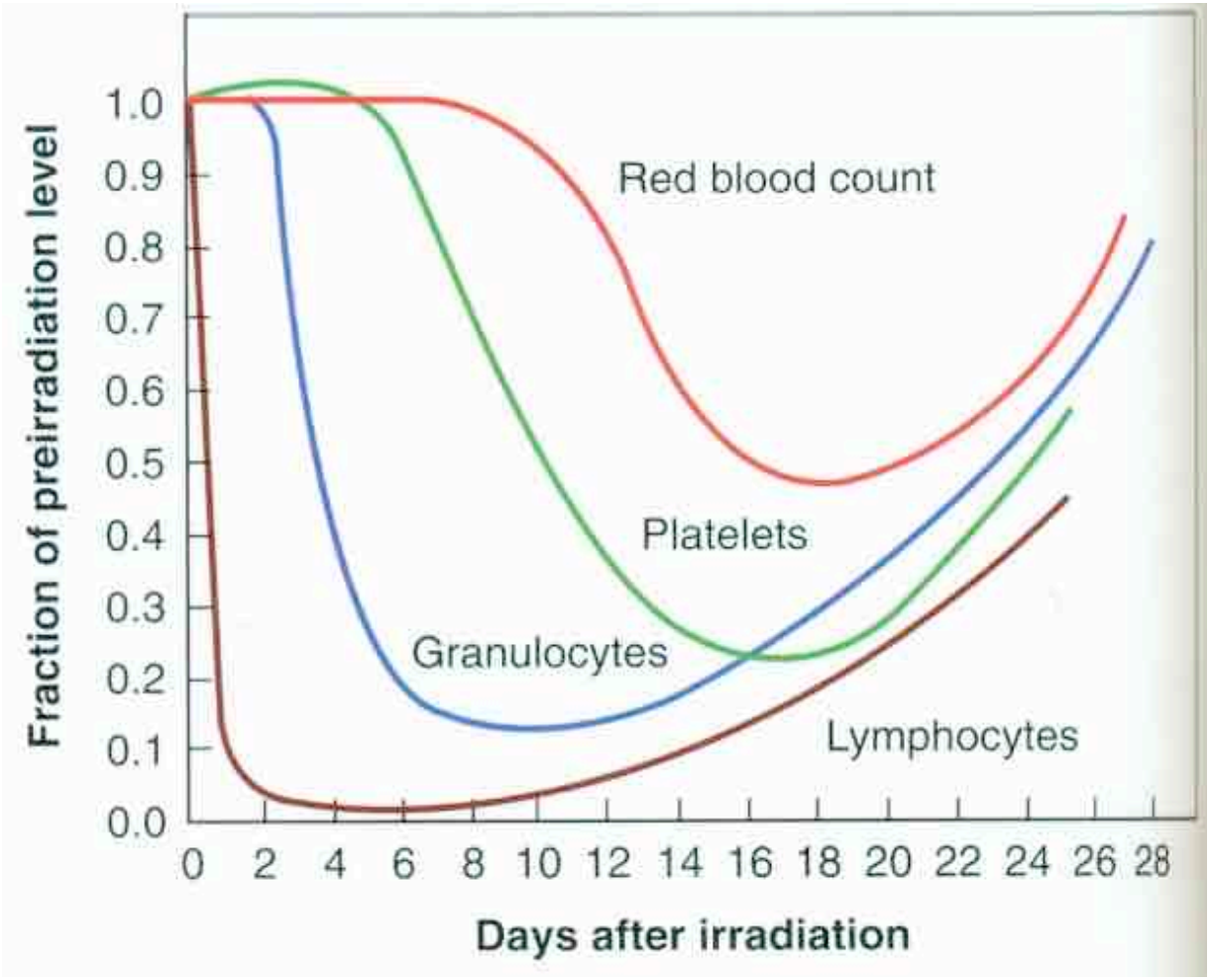
A Typical Clonogenic Cell Survival Curve

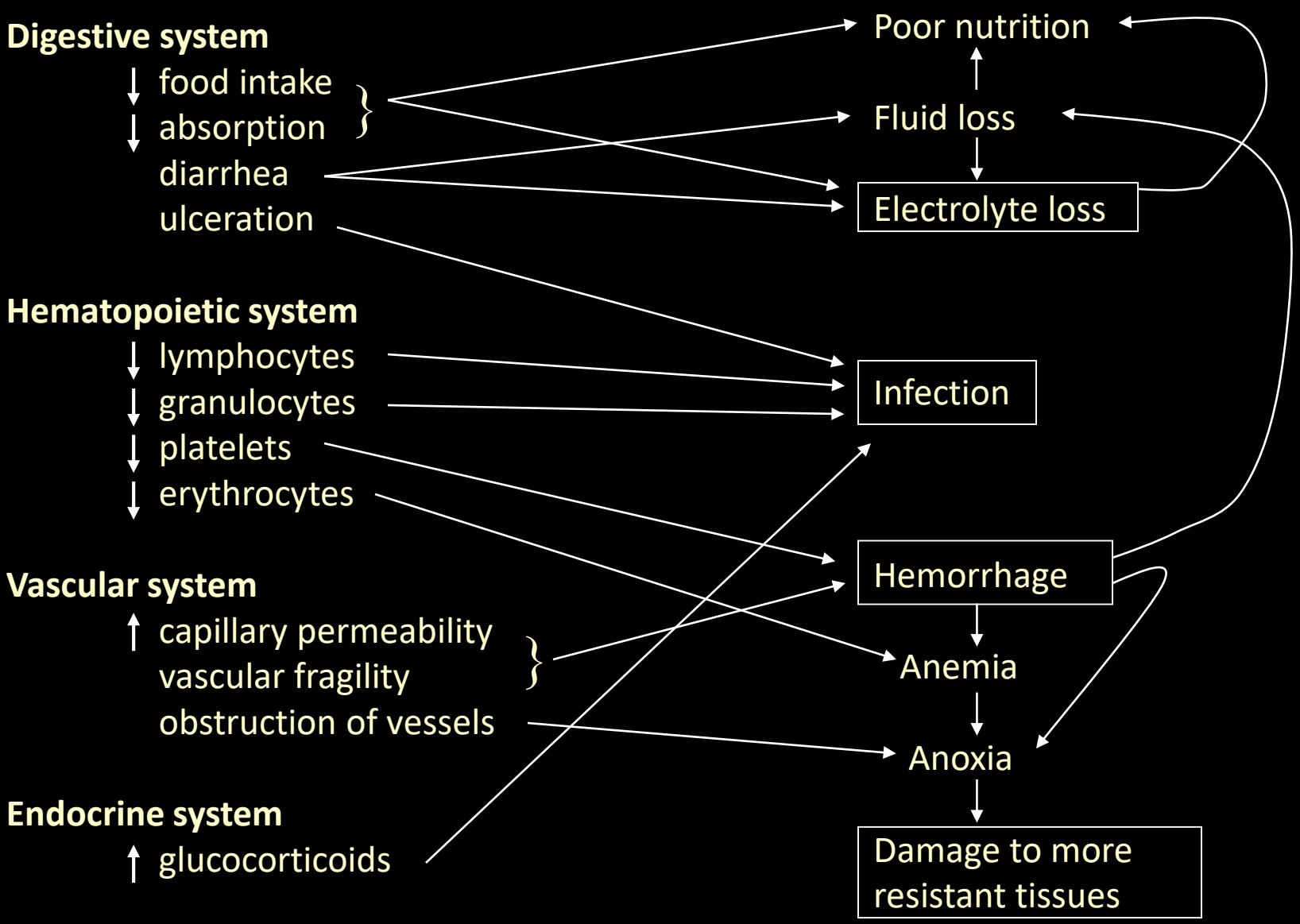


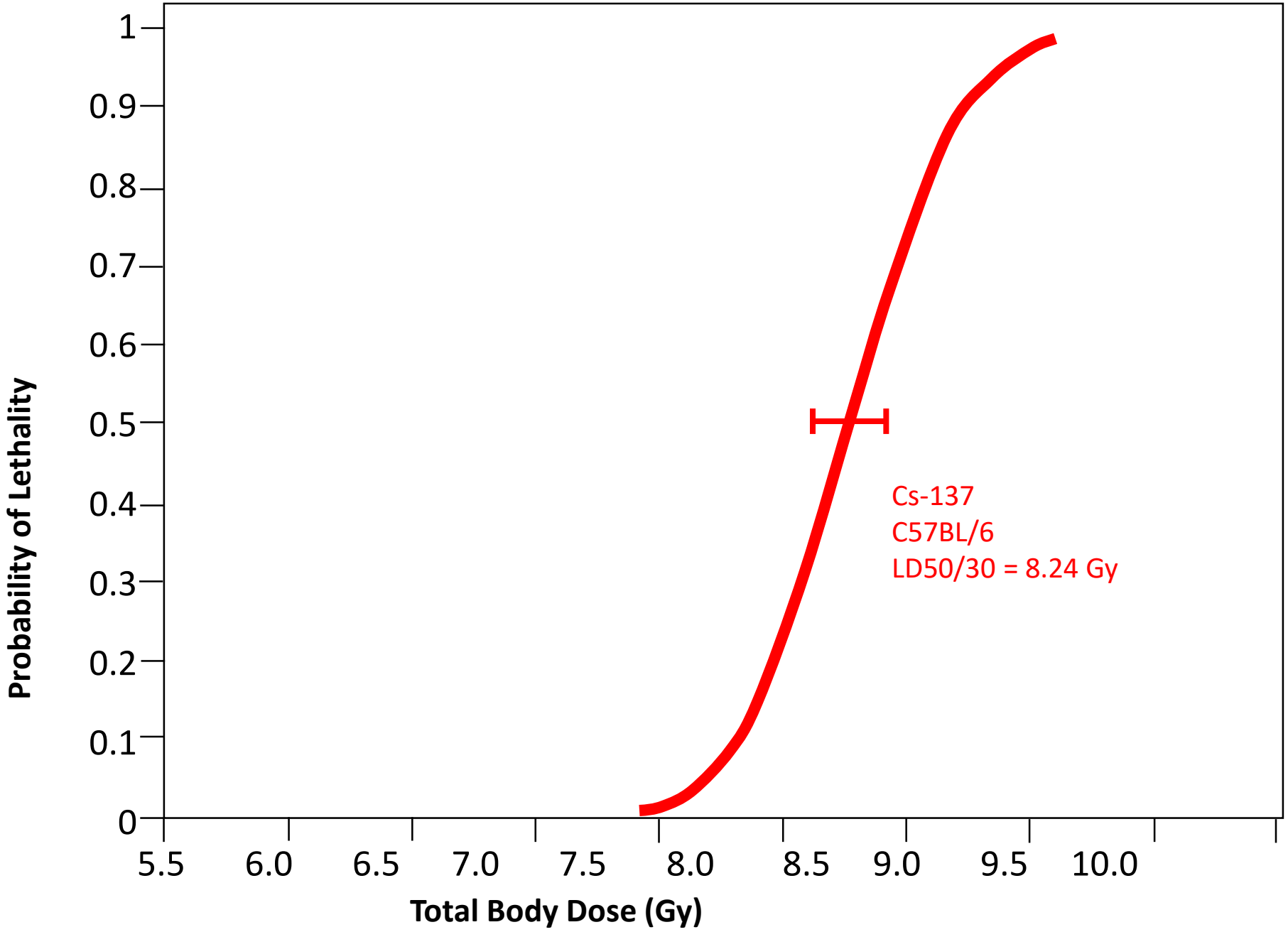

1.0
10^{-1}
10^{-2}
Surviving fraction
$RBE_{SF=0.1} = \frac{3.5}{0.9} \approx 4$
$RBE_{SF=0.01} = \frac{5.9}{1.9} \approx 3$
2
4
6
8
10
Dose

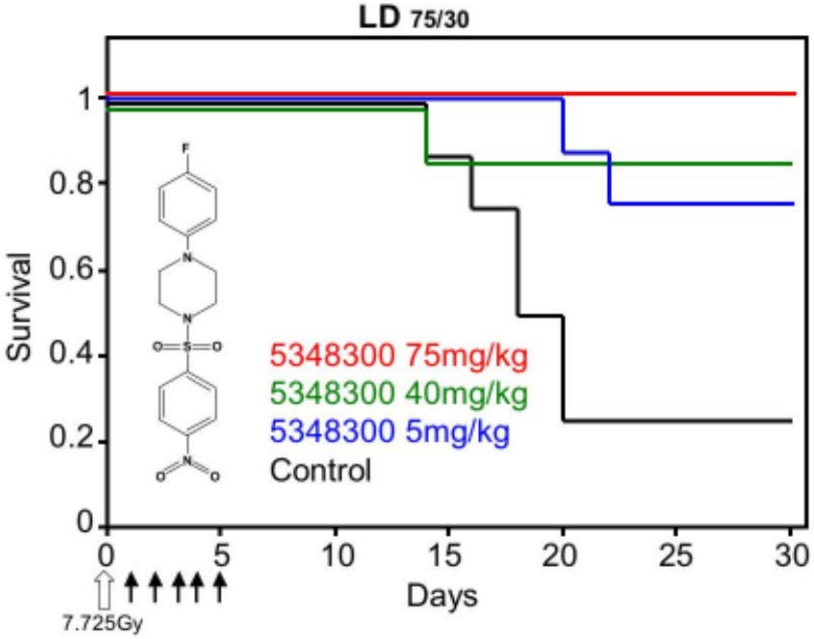


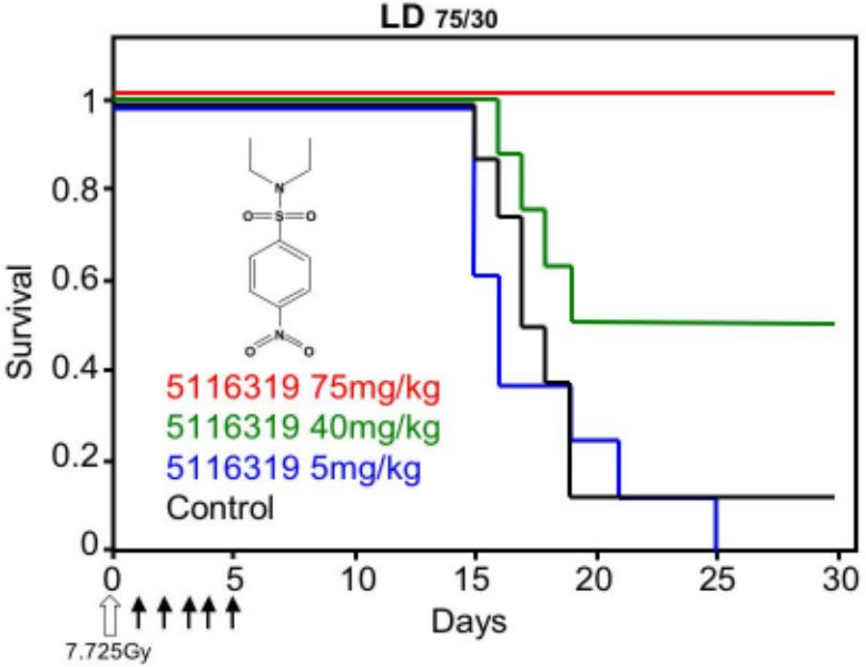

Co-60
Xoft
Surviving Fraction
1
0.1
0.01
0.001
0
2
4
6
8
Dose (Gy)
RBE (SF37) ≈ 2.3
RBE (SF10) ≈ 1.8
RBE (SF1) ≈ 1.5

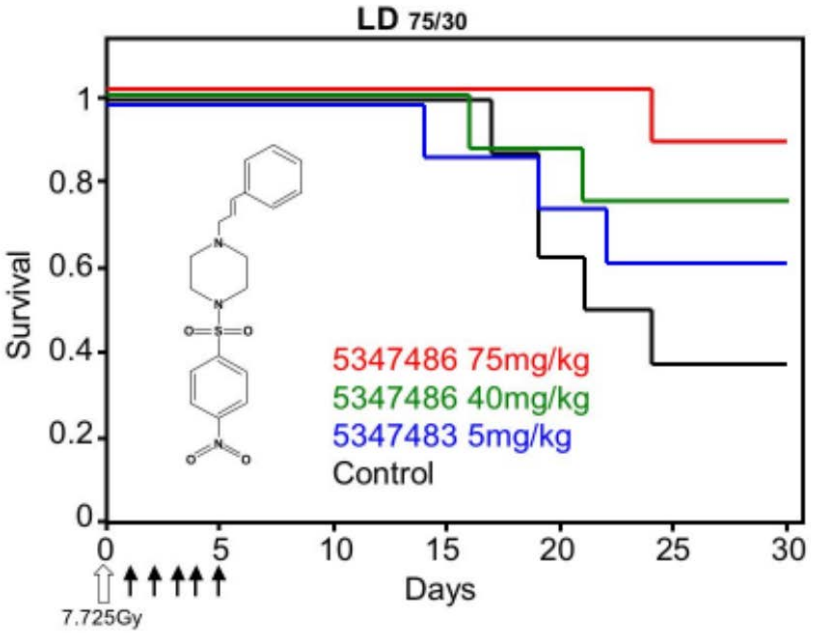

Fraction of preirradiation level
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Red blood count
Platelets
Granulocytes
Lymphocytes
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days after irradiation


Digestive system
↓ food intake
↓ absorption
diarrhea
ulceration
Hematopoietic system
↓ lymphocytes
↓ granulocytes
↓ platelets
↓ erythrocytes
Vascular system
↑ capillary permeability
vascular fragility
obstruction of vessels
Endocrine system
↑ glucocorticoids
Poor nutrition
Fluid loss
Electrolyte loss
Infection
Hemorrhage
Anemia
Anoxia
Damage to more resistant tissues

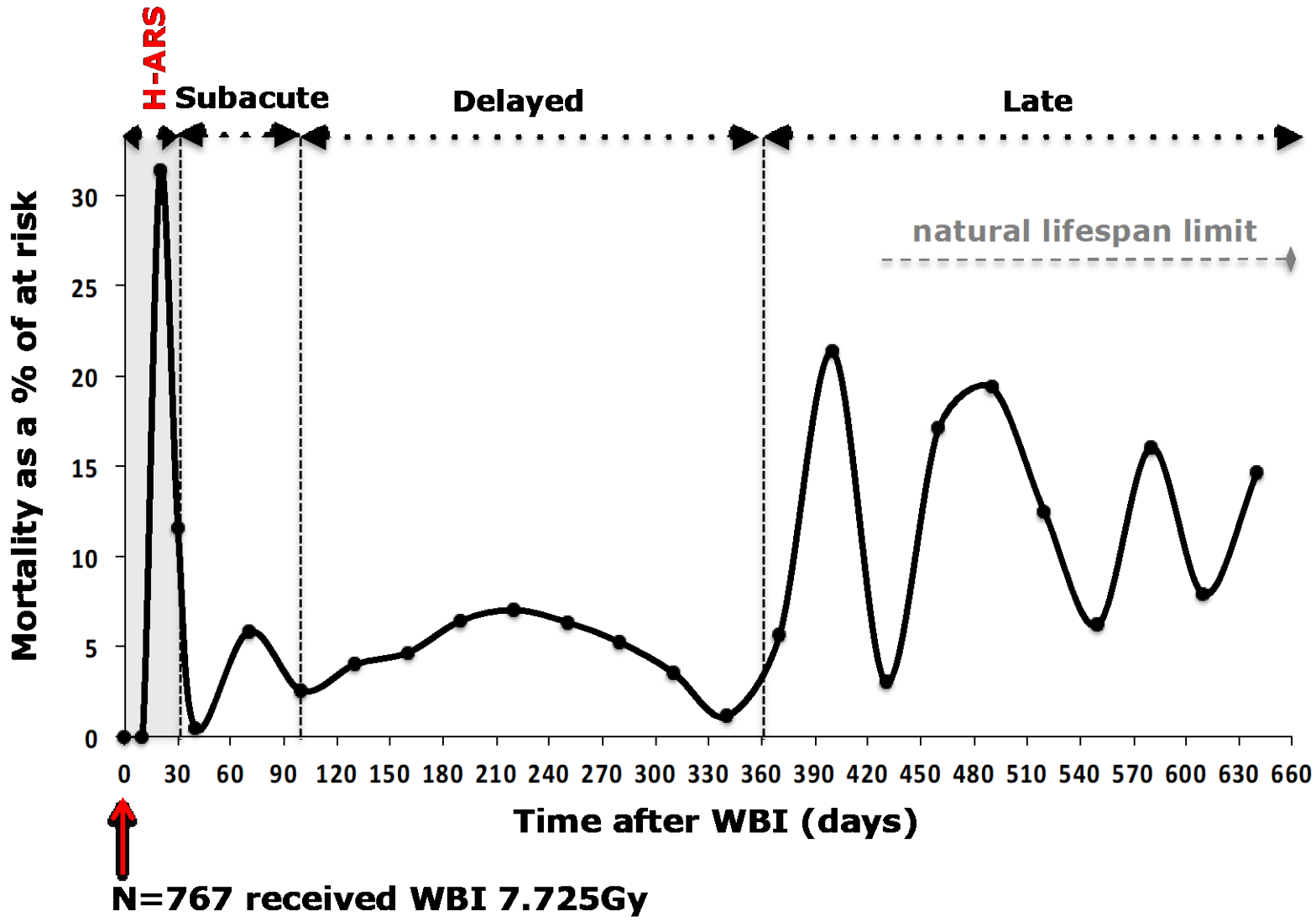

Probability of Lethality
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
Total Body Dose (Gy)
Cs-137
C57BL/6
LD50/30 = 8.24 Gy


LD 75/30
Survival
Days
5348300 75mg/kg
5348300 40mg/kg
5348300 5mg/kg
Control
7.725Gy

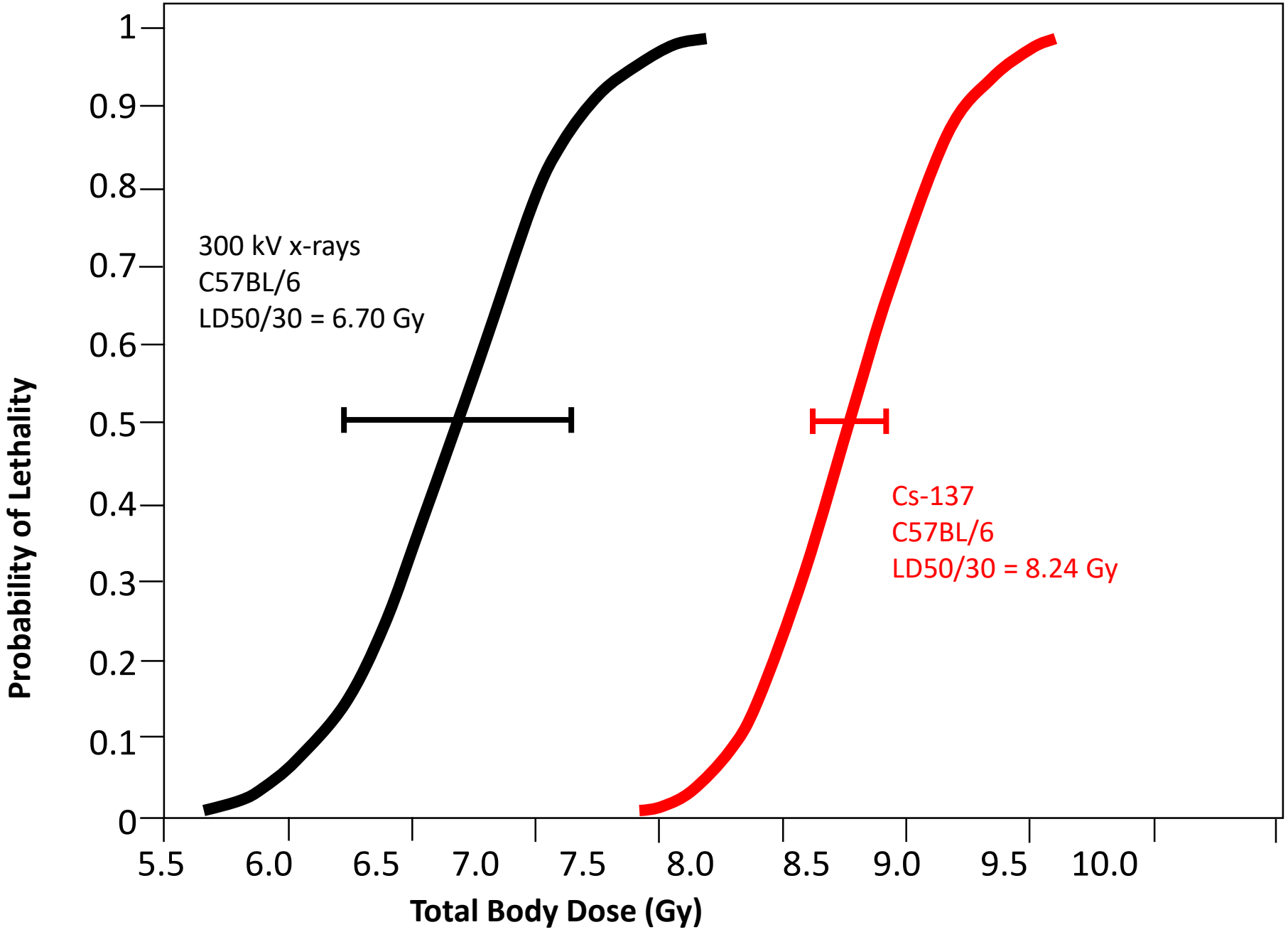

LD 75/30
Survival
Days
5116319 75mg/kg
5116319 40mg/kg
5116319 5mg/kg
Control
7.725Gy


LD 75/30
Survival
Days
5347486 75mg/kg
5347486 40mg/kg
5347483 5mg/kg
Control
7.725Gy

Patterns of mortality post-rescue of WBI



Micewicz et al. in press


Probability of Lethality
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
Total Body Dose (Gy)
300 kV x-rays
C57BL/6
LD50/30 = 6.70 Gy
Cs-137
C57BL/6
LD50/30 = 8.24 Gy

x-ray energy	RBE to CS-137	Relative dose increase	system	endpoint	citation	notes	Model
320 kV (1mm Cu HVL)		1.16	Bone marrow	Clonogenic growth post in vivo IR	Belley et al. 2015		animals
320 V (4mm Cu HVL)		1.07	Bone marrow	Clonogenic growth post in vivo IR	Belley et al. 2015		animals
320 kV	0.763		Splenocytes TBI	cytotoxicity	Scott et al. 2013		animals
320 kV	1.346		Bone marrow TBI	cytotoxicity	Scott et al. 2013		animals
160 kV	See note		Bone marrow	Bone marrow transplant reconstitution	Gibson et al. 2015	Due to the statistically significant variability in B, T, myeloid cell reconstitution between the X-ray and 137Cs sources of irradiation, we accept the null hypothesis. We conclude that although both sources were efficient at ablating endogenous bone marrow sufficiently to enable stem cell engraftment, there are distinct physiologic responses that should be considered prior to choosing the optimal source for use in a study. In addition, irradiation using the 137Cs source was associated with lower overall morbidity.	animals
300 kV (1.65mm Cu HVL)	1.11		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 100 cells/circumference ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.08		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 10 cells/circumference for ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.07		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 1 cells/circumference for ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.00		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 100 cells/circumference for a single fraction of 11.36 Gy	animals
300 kV (1.65mm Cu HVL)	1.00		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 10 cells/circumference for a single fraction of 11.36 Gy	animals
300 kV (1.65mm Cu HVL)	1.08		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 1 cells/circumference for a single fraction of 11.36 Gy	animals
320 kV (HVL 1mm Cu)	1.5		HBEC-13	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 1mm Cu)	1.6		HBEC-2	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 3.7mm Cu)	1.2		HeLa	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 3.7mm Cu)	1.5		A549	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
300 kV (HVL 3mm Cu)	Approx 1.23		C57BL/6	LD50/30	UCLA radonc		animals

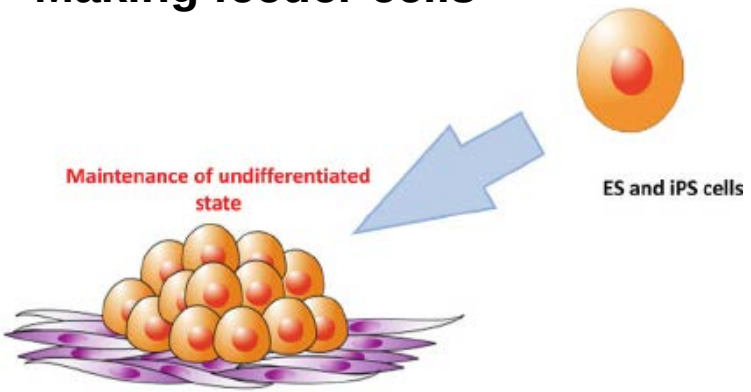
UC-wide Survey Results

Approximately half the studies involve *in vitro* (cells) and half involve *in vivo* (rodents) irradiations.

The largest single proportion (41%) of the *in vitro* irradiations was for production of feeder cells to support growth of growth-factor-dependent cells.

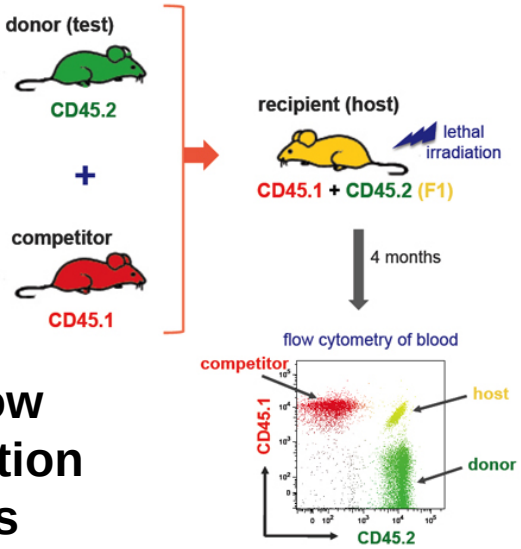
The largest single proportion (37%) of the *in vivo* irradiations was for bone marrow ablation in preparation for transplantation experiments.

Making feeder cells

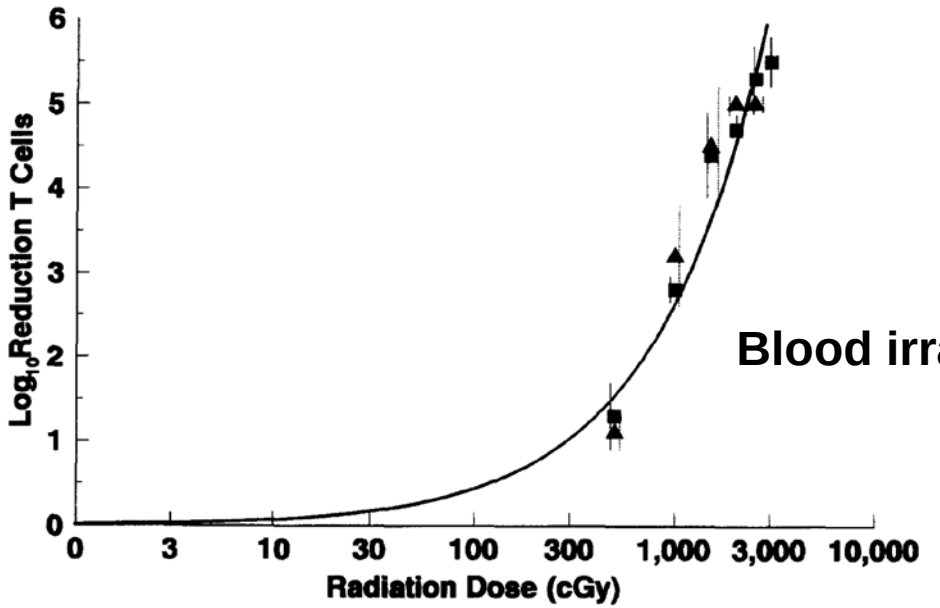


Feeder cells

Bersenev 2011



Bone marrow transplantation experiments



Blood irradiations to prevent GVHD

Pelszynski, et al. 1994

Conclusions

- **Biology is a dynamic system**
  There is always a response

- **Biological dose ≠ physical dose**
  In general, x-rays (energies equal to or below 320 kV) are more biologically effective than Cs-137 gamma rays suggesting that lower doses of x-rays will be required to achieve the same biological endpoint as Cs-137 gamma rays. Conversely, less penetration in some targets may reduce dose effects.

- **Different endpoints => different RBE's**
  It is difficult to provide a simple conversion factor for equating x-ray effects to Cs-137 effects because RBE depends on multiple factors including x-ray peak energy, x-ray energy spectrum (filtration), biological system, endpoint, etc.

- **Different IR sources & conditions => different cellular responses**
  Standardization – Unlike the single gamma energy of Cs-irradiators, output energies of the x-irradiators cited in the literature are diverse due to variations in x-ray tubes and filtration utilized; in some cases, the quality of the beam (HVL) is not described.

- **ID of the IR may not matter much or at all in some cases**
  Each experiment will need to be individually calibrated when converting from Cs-irradiators to x-irradiators and the effort and resources required will depend on the precision of the effect desired. For example, in cases where inactivation of support cell proliferation or unwanted cell activity is desired, as in the case of production of feeders, the specificity of the absolute dose may not be as critical as ascertaining animal lethality dose.

The Key Take-home-message:

Expect a response but know that it might not be what you expected.